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Brief report
A study of the prevalence and associations of subchondral bone marrow lesions in the knees of healthy, middle-aged women[1]

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Summary

Objective: Bone marrow lesions (BMLs) have been shown to be associated with pain and progression of knee osteoarthritis (OA) in those with disease. The natural history of BMLs in a healthy population and their role in the pathogenesis of OA are unknown. The aim of this study was to determine the risk factors for BMLs in healthy subjects and the association of BMLs with knee structure.

Methods: One hundred and seventy-six healthy, adult women with no history of knee injury, or clinical knee OA had magnetic resonance imaging performed on their dominant knee to assess BMLs, tibiofemoral cartilage defects, tibial cartilage volume and bone area.

Results: Thirteen percent of subjects had knee BMLs. The prevalence was higher in the medial tibiofemoral compartment. There was a significant positive association between BMLs and cartilage defects after adjusting for the potential risk factors: age, height, weight and cartilage volume [odds ratio (OR) 1.78 (95% confidence interval [CI] 1.12, 2.82), $P = 0.01$]. BML was positively associated with tibial plateau bone area in the lateral compartment [OR 1.67 (95% CI 1.02, 2.71), $P = 0.04$]. There was no significant association between BMLs and cartilage volume. Independent risk factors for BMLs after adjustment were increasing height [OR 1.18 (95% CI 1.02, 1.36), $P = 0.02$ for lateral compartment] and weight [OR 1.04 (95% CI 1.01, 1.08), $P = 0.005$ for total knee].

Conclusion: These data support that BMLs are present in a similar distribution to tibiofemoral knee OA. Their presence is associated with risk factors (height and weight) for knee OA, and the early structural changes of knee OA in subjects without knee pain and thus no clinical disease. Longitudinal studies will clarify whether BMLs relate to the pathogenesis of clinical knee OA.

Key words: Osteoarthritis, Cartilage, Bone marrow lesions, Weight, Body mass index.

Introduction

Osteoarthritis (OA) is the most common joint disease of the elderly and the major cause of disability in people over the age of 65[1]. Despite its prevalence and the frequent disability with which it is associated, the etiology and risk factors involved in the pathogenesis of OA have not been fully elucidated. Subsequently, limited preventive strategies have been identified to modify predisposing factors.

In part, progress in understanding OA etiology has been limited by the inability to assess joint structure directly and non-invasively. Recently, the use of magnetic resonance imaging (MRI) has permitted direct visualization of all components of the joint simultaneously[2,3] and to examine different structural components of the knee. There is evidence that subchondral bone marrow lesions (BMLs) imaged on MRI are involved in the pathogenesis of OA[4–6]. These extend from the medullary space of the bone into the subchondral region. There is evidence that these lesions are clinically important since they have been shown to be positively associated with knee pain[6] and to be associated with progression of knee OA[5].

Most previous studies have examined BMLs, bone marrow edema lesions or bone bruises in patients with OA[4,6,7] or in those who have undergone MRI after trauma or for investigation of internal knee derangement[8,9]: there are few studies investigating specifically healthy,

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asymptomatic people[10,11]. In healthy subjects with no OA, traumatic injuries of the knee can result in subchondral bone edema lesions[12,13]. The current study aims to determine the prevalence and possible risk factors for subchondral BMLs in the knee present in healthy women with no history of knee injury, or clinical knee OA, and to examine whether their presence relates to other knee structures.

Patients and methods

SUBJECTS

Eligible participants were part of a previous cross-sectional study examining androgens in women, having been recruited from a database established from the electoral roll in the southern Australian state of Victoria between April 2002 and August 2003[14]. Of the 1423 participants aged 18–75 years who participated in the original study, 227 women were eligible by way of being in the desired age-group (40–67 years), not having had a hysterectomy and having agreed to be recontacted about participation in further research studies. Subjects were further excluded if they had had any of the following: a clinical diagnosis of knee OA as defined by American College of Rheumatology criteria[15]; knee pain lasting for >24 h in the last 5 years (2); a previous knee injury requiring non-weight bearing treatment for >24 h or surgery (including arthroscopy) (1); a malignancy; or they were unable to complete the study (e.g., proposed relocation); or they had a history of any form of arthritis diagnosed by a medical practitioner; or they had a contraindication to MRI (7) including pacemaker, metal sutures, presence of shrapnel or iron filings in the eye, or claustrophobia. The reasons for non-participation of the other women were the following: could not be contacted ($N = 27$); no longer interested in participating ($N = 9$); too far to travel ($N = 3$); recent hysterectomy ($N = 2$). One hundred and seventy-six eligible women agreed to participate. The study was approved by the Southern Health Human Research and Ethics Committee and the Monash University Human Research and Ethics Committee, Clayton, Victoria, Australia. All participants gave written informed consent.

ANTHROPOMETRIC DATA

At the time of the original cross-sectional study (2002–2003) each participant attended for height and weight measurements. From these data, body mass index (BMI) was calculated [weight (kg)/height^2 (m^2)].

MRI AND THE MEASUREMENT OF CARTILAGE VOLUME, DEFECTS, BONE AREA AND BMLS

Each woman attended for MRI of her dominant knee (defined as the lower limb from which the subject stepped off from when initiating gait) between October 2003 and August 2004. Knees were imaged in the sagittal plane on a 1.5-T whole body magnetic resonance unit (Philips) using a commercial transmit–receive extremity coil. The following sequence and parameters were used: a T1-weighted fat suppressed three-dimensional (3D) gradient recall acquisition in the steady state; flip angle, 55°; repetition time, 58 ms; echo time, 12 ms; field of view, 16 cm; 60 partitions; 513 × 196 matrix; one acquisition time, 11 min 56 s. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 × 0.83 mm (512 × 196 pixels). In addition, a T2-weighted fat-saturated acquisition with a repetition time of 2200 ms, echo time of 20/80 ms, a slice thickness of 3 mm, a 0.3 interslice gap, one excitation, a field of view of 11–12 cm, and a matrix of 256 × 128 pixels were also obtained.

The volumes of the individual cartilage plates (medial and lateral tibial) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on each section. These data were re-sampled by bilinear and cubic interpolation (area of 312 and 312 μm and 1.5 mm thickness, continuous sections) for the final 3D rendering. The volume of the particular cartilage plate was determined by summing the pertinent voxels within the resultant binary volume. Two trained observers read each MRI independently, and the mean value was used, as previously described[3,16]. Intraobserver and interobserver reliability for medial and lateral cartilage volume measurements were obtained using intraclass correlation coefficients (ICCs). These ranged from 0.914 to 0.964.

Medial and lateral cross-sectional areas of tibial plateau were determined by creating an isotropic volume from the input images which were reformatted in the axial plane using the software program Osiris as described[3]. Areas were directly measured from these images by a single reader in duplicate. Intraobserver reliability for medial and lateral tibial area was assessed using ICCs. These were 0.992 and 0.994, respectively.

Cartilage defects were graded on the magnetic resonance (MR) images with a classification system that has been previously described[17–19], in the medial and lateral tibial and femoral cartilages. The grading is as follows: grade 0, normal cartilage; grade 1, focal blistering and intracartilaginous low-signal intensity area with an intact surface and bottom; grade 2, irregularities on the surface or bottom and loss of thickness of less than 50%; grade 3, deep ulceration with loss of thickness of more than 50%; grade 4, full-thickness cartilage wear with exposure of subchondral bone. A cartilage defect also had to be present in at least two consecutive slices. The cartilage was considered to be normal if the band of intermediate signal intensity had a uniform thickness. The cartilage defect score for a compartment was calculated by summing the grades of cartilage defect in the tibial and femoral cartilage plates in that compartment. Intraobserver reliability (expressed as ICC) was 0.90 for the medial tibiofemoral compartment and 0.89 for the lateral tibiofemoral compartment. Interobserver reliability was assessed in 50 MR images and yielded an ICC of 0.90 for the medial tibiofemoral compartment, and 0.85 for the lateral tibiofemoral compartment[18].

BMLs were defined as areas of increased signal intensity adjacent to subcortical bone in either the distal femur or the proximal tibia[4]. Two trained observers, who were blinded to patient characteristics, together assessed the presence of lesions for each subject using the method described by Felson *et al.*[6] The presence or absence of BMLs was determined. A lesion was identified as being present if it appeared on two or more adjacent slices. Lesions were classified as large if they encompassed at least one-quarter of the medial/lateral compartment, in accordance with previous work[6]. The locations of evident lesions were categorized into one of the four sites in the subchondral bone (medial and lateral femoral condyle, medial and lateral tibial condyle). The reproducibility for determination of the BMLs was assessed using 60 randomly selected knee MRIs (κ value 0.88, $P < 0.001$).

Descriptive statistics for the characteristics of the subjects were tabulated. Relationships between BMLs and risk factors for OA were assessed by calculating univariate

and multivariate odds ratios (ORs). This was performed for lesions in the total tibiofemoral compartment, and the medial and lateral compartments separately. Relationships between BMLs and other structures in the knee were assessed using crude and adjusted ORs. *P*-values of less than 0.05 were considered to be statistically significant. All analyses were performed using the SPSS statistical package (standard version 12.0.1, SPSS, Chicago, IL).

Results

The characteristics of the 176 participants, women aged between 40 and 67 years (mean 52.3 years), are presented in Table I. Subjects with BMLs had higher weight, BMI, and higher medial and total tibiofemoral cartilage defect scores than those without BMLs.

Twenty-three (13.1%) subjects had BMLs in the subchondral bone of the knee (Table II). Thirteen (7.4%) subjects had large BMLs. Whilst BMLs were present in the medial compartment in 16 subjects (point prevalence 9.1%, 95% confidence intervals (CIs) for this estimate are 4.8%, 13.4%) and in the lateral compartment in seven subjects (point prevalence 4.0%, 95% CIs for this estimate are 1.1%, 6.9%). The test for difference in proportions, McNemars' test, suggested that this difference was significant ($P = 0.03$).

The associations between the presence of BMLs and severity of knee structural change, as measured by cartilage volume, cartilage defect score and tibial plateau bone area, were examined (Table III). In univariate analyses, the presence of BMLs was positively associated with tibial cartilage volume in the medial compartment. However, the presence of BMLs was not significantly associated with tibial cartilage volume in any compartment after adjusting for age, height, weight and tibial bone area. BMLs were more likely to be present in those with higher medial and total tibiofemoral cartilage defect scores in both univariate and multivariate analyses in which adjustment was made for age, height, weight, and cartilage volume. BMLs were also more likely to be present in the lateral compartment in those with larger lateral tibial bone area in both univariate and multivariate analyses. There were similar findings when the relationship between the presence of large BMLs and knee structure was examined (results not shown).

The relationships between risk factors of OA and the presence of BMLs are presented in Table IV. Age was not significantly associated with the presence of BMLs. In univariate analyses, height was positively associated with the presence of BMLs in the lateral compartment. This association continued to have significance when adjusted for age and weight. Weight was positively related to BMLs in the medial compartment as well as the total knee in both univariate and multivariate analyses. BMI was positively related to BMLs in the medial compartment and total knee after adjusting for age.

Discussion

In this study of healthy, pain free, middle-aged women, free of joint disease, we found that BMLs were present in 13% of subjects, with large lesions (i.e., encompassing at least one-quarter of the medial/lateral compartment) being found in 7% of subjects. The prevalence of BMLs was higher in the medial tibiofemoral compartment. Although there was no significant association between the presence of BMLs and articular cartilage volume, BMLs were more likely to be present in those with higher cartilage defect scores and higher lateral tibial plateau bone area, both markers of early degenerative change in the knee. Independent risk factors for BMLs were increasing weight and BMI.

Previously, the correlates of BMLs were described in populations who were mixed with respect to OA and pain[5,6,10,11,20]. In this study we found that 13% of healthy, asymptomatic subjects had knee BMLs on MRI. This is somewhat lower than the prevalence described by Sowers *et al.* who found that 39% of knees in 30 subjects who were pain free and had no knee OA (Kellgren Lawrence <2) had evidence of BMLs[10]. This may be explained by a less stringent definition of BMLs, where smaller lesions than described in our study were classified as present. We did, however, find that 7% of our subjects had evidence of large BMLs. This finding is compatible with Sowers *et al.*[10] who also found that four (11%) of 60 knees had BMLs of similar size to the large lesions measured in this study. Felson

Table I
Characteristics of study participants

	Total ($N = 176$)	Subjects without BMLs ($N = 153$)	Subjects with BMLs ($N = 23$)	*P*-value*
Age at MRI (years)	52.3 (6.6)	52.4 (6.7)	51.6 (6.5)	0.60
Height (cm)	164.0 (6.5)	163.9 (6.3)	164.8 (7.5)	0.56
Weight (kg)	72.7 (14.1)	71.4 (13.0)	80.8 (18.0)	0.003
BMI (kg/m^2)	27.1 (5.5)	26.7 (5.2)	29.8 (6.6)	0.04
Tibial cartilage volume (cm^3)				
Medial	1.5 (0.3)	1.5 (0.3)	1.6 (0.3)	0.14
Lateral	1.8 (0.3)	1.8 (0.3)	1.8 (0.4)	0.65
Total	3.3 (0.5)	3.3 (0.5)	3.4 (0.6)	0.30
Tibial plateau bone area (cm^2)				
Medial	19.7 (1.7)	19.7 (1.6)	20.1 (2.0)	0.28
Lateral	12.4 (1.3)	12.3 (1.3)	12.7 (1.8)	0.27
Total	32.1 (2.6)	32.0 (2.4)	32.8 (3.4)	0.27
Tibiofemoral cartilage defect scores†				
Medial	1 (1, 4)	1 (1, 4)	2 (1, 4)	0.29
Lateral	1 (1, 3)	1 (1, 3)	1 (1, 3)	0.095
Total	2 (2, 6)	2 (2, 6)	3 (2, 6)	0.24

Values reported as mean (SD). **P*-value indicates significance of difference between subjects without BMLs and those with BMLs. †Median (range), comparison by Somers' *d* test.

Table II
The distribution and severity of BMLs in the population

	No BMLs	BMLs	Large BMLs
Medial compartment			
Femoral condyle	164	5	7
Tibial condyle	171	2	3
Any BML	160	7	9
Lateral compartment			
Femoral condyle	171	2	3
Tibial condyle	174	1	1
Any BML	169	3	4

et al.[6] found that whilst the prevalence of BMLs was in 30% of people with painless radiographic knee OA, only 2% had large BMLs. This cohort was significantly different from the other two, in that they were older, had a lower proportion of women, and had radiographic knee OA defined by osteophytes.

Our data showed that BMLs were associated with more severe cartilage defects. The positive association between BMLs and cartilage defects in the total knee is the natural extension of other studies performed in subjects with radiological evidence of knee OA, where cartilaginous defects in the tibiofemoral compartment correlated positively with ipsilateral tibiofemoral BMLs[21], and the mean depth and cross-sectional area of subchondral BMLs increased with increasing grade of articular cartilage defects[22]. Previous work has shown the positive association between early degenerative knee disease, in the form of prevalence and severity of cartilage defects, and tibial bone area[18]. Libicher *et al.* found that in an induced animal model of OA that the first sign of change in the development of OA was subchondral bone marrow edema, which preceded any discernable cartilage changes[23]. These data suggest that BMLs are involved in the pathogenesis of knee OA, occurring in the continuum from the healthy knee to one with OA.

The association between BMLs and cartilage defects may be important since both have been shown to relate to subsequent cartilage loss. Cartilage defects, present in healthy, asymptomatic subjects with no radiological evidence of knee OA, predict cartilage loss, with those with defects having a twofold increased rate of cartilage loss[17]. The emerging data suggest that cartilage defects occur early in people who subsequently lose cartilage and that a reduction in cartilage volume predates any radiological changes so that by the time the earliest radiological changes are observed up to 13% of knee cartilage is already lost[24]. In OA, it has also been shown that change in severity of BMLs is positively associated with change in the urinary excretion of C-terminal cross-linking telopeptide of type II collagen, which is a biological marker of cartilage degradation, and linked to the radiological worsening of knee OA[25]. Large BMLs (lesions encompassing at least one-quarter of the medial/lateral compartment) have been associated with the progression of radiological knee OA, defined as reduction in joint space narrowing[5]. Our study found that BMLs are related to what appear to be the earliest structural change in cartilage, namely cartilage defects[26]. Longitudinal studies are required to confirm the relationship with cartilage volume loss.

We found that the presence of BMLs was associated with increasing BMI and weight. There is little previous data on risk factors for BMLs. Consistent with our findings, a study by Lo *et al.*[11] found that subjects with lesions were more likely to have a higher BMI than subjects without BMLs, albeit in a population with both OA and no OA. Most previous work has examined the relationship between BMLs and biomechanical factors. For example, BMLs have been shown to be associated with static malalignment[5] and related to increased bone mineral density (BMD) locally[11], using the BMD medial:lateral ratio. These data suggest that BMLs may be related to loading. In this study, we were not able to measure knee alignment which has been shown to provide insight into relationship between abnormal loading in the knee with the presence of lesions[5].

This study has a number of limitations. The participants in our study are females and although knee OA occurs more often in females, men may be more likely to sustain knee trauma which may affect the prevalence of BMLs. The study participants are also likely to represent the more health conscious of all those who were initially recruited into the Healthy Women's Study, since our participants agreed to be contacted at a later date for further research purposes. Although this may have affected the estimates of knee cartilage volume, tibial bone area, cartilage defects and BMLs, it is unlikely that this had much effect on the relationship between these variables. The analysis is cross-sectional, so cause and effect relationships of the variables cannot be investigated. The strength of this study is the conservative method used for assessing BMLs in healthy asymptomatic

Table III
Relationships between structural changes in the knee and BMLs

	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Tibial cartilage volume*				
Medial BMLs	6.46 (1.09, 38.39)	0.04	5.73 (0.72, 45.38)	0.10
Lateral BMLs	0.63 (0.07, 6.01)	0.69	0.15 (0.01, 2.36)	0.18
BMLs in total knee	1.51 (0.69, 3.27)	0.30	1.22 (0.51, 2.92)	0.66
Tibiofemoral cartilage defects†				
Medial BMLs	6.46 (1.04, 38.39)	0.04	3.51 (1.08, 11.42)	0.04
Lateral BMLs	1.17 (0.22, 6.26)	0.85	1.02 (0.17, 6.12)	0.98
BMLs in total knee	1.51 (0.69, 3.27)	0.30	2.12 (0.83, 5.45)	0.12
Tibial plateau bone area‡				
Medial BMLs	1.19 (0.88, 1.62)	0.26	1.21 (0.88, 1.66)	0.25
Lateral BMLs	1.67 (1.02, 2.71)	0.04	1.67 (1.02, 2.71)	0.04
BMLs in total knee	1.13 (0.96, 1.33)	0.15	1.14 (0.96, 1.35)	0.13

*Odds of a BML being present for a 1 ml increase in cartilage volume adjusted for age, height, weight, and tibial bone area. †Odds of a BML being present if cartilage defects are present in either the tibial or femoral cartilages, adjusted for age, height, weight, and tibial cartilage volume. ‡Odds of a BML being present for a 1 cm^2 increase in tibial plateau bone area, adjusted for age and BMI.

Table IV
Risk factors for BMLs

	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age (years)*				
Medial BMLs	0.97 (0.90, 1.05)	0.51	0.96 (0.89, 1.05)	0.40
Lateral BMLs	1.00 (0.89, 1.12)	0.96	1.05 (0.92, 1.18)	0.48
BMLs in total knee	0.98 (0.92, 1.05)	0.59	0.98 (0.92, 1.06)	0.64
Height (m)*				
Medial BMLs	0.96 (0.89, 1.04)	0.34	0.95 (0.87, 1.03)	0.18
Lateral BMLs	1.17 (1.03, 1.33)	0.02	1.18 (1.02, 1.36)	0.02
BMLs in total knee	1.02 (0.95, 1.09)	0.56	1.01 (0.94, 1.08)	0.83
Weight (kg)*				
Medial BMLs	1.05 (1.01, 1.09)	0.01	1.05 (1.02, 1.09)	0.004
Lateral BMLs	1.02 (0.97, 1.07)	0.41	1.01 (0.96, 1.07)	0.68
BMLs in total knee	1.04 (1.01, 1.08)	0.01	1.04 (1.01, 1.08)	0.005
BMI (kg/m^2)†				
Medial BMLs	1.14 (1.04, 1.24)	0.004	1.14 (1.04, 1.24)	0.004
Lateral BMLs	0.99 (0.86, 1.14)	0.90	0.99 (0.86, 1.14)	0.90
BMLs in total knee	1.10 (1.02, 1.19)	0.01	1.10 (1.02, 1.19)	0.01

*OR of a BML being present per unit increase in respective variable, adjusted for age, height, and weight. †OR adjusted for age.

subjects. Our study used two adjacent MR images to classify a BML with a minimum grade, ensuring that only definite lesions were included, in contrast to previous studies used which required an abnormality to be present in one.

In summary, we have found BMLs are present in the knees of middle-aged women who have no significant knee pain or injury. BMLs were associated with cartilage defects in the total medial and lateral tibiofemoral compartments. Thus the earliest structural changes of OA visible by clinical MRI are associated with BMLs, supporting a role for BMLs in the pathogenesis of knee OA prior to development of clinical disease and suggest that obesity may be an important risk factor for BMLs. Longitudinal studies will clarify whether this is indeed the case.

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